seemingly contradictory interactions among Bcl-2 proteins and their contributions to mitochondrial outer membrane permeabilization as inhibitors, promoters, or sensitizers of apoptosis.

906-Pos Board B706

Robustness Portraits of Diverse Biological Networks Conserved Despite Order-Of-Magnitude Parameter Variation

Anthony R. Soltis, **Jeffrey J. Saucerman**.

Many biological networks are robust to a wide variety of internal and external perturbations, yet fragile to a select group of uncommon perturbations. Because fragile system modes are highly sensitive to certain biochemical parameters, it is unclear how precisely biochemical parameters must be known a priori in order to accurately predict the robustness portrait of a system. Here, we examined a previously well-characterized model of the cardiac beta-adrenergic signaling network and found that its robustness portrait was well conserved, even when parameters were rounded to their nearest 1-2 orders of magnitude ($r = 0.82$ and 0.63, respectively). This analysis was then extended to 10 additional networks of diverse biological processes, including E. Coli chemotaxis, stem cell differentiation, and cytokine signaling. Nine out of 10 of these networks exhibited conserved robustness portraits ($r > 0.75$) despite systematic order-of-magnitude variations in their biochemical parameters. These results illustrate the ability to predict both fragile and robust aspects of diverse biological networks despite imprecise biochemical parameters. Additionally, this work suggests a strategy from which approximate models can be used to prioritize experiments towards fragile system modes, leading to efficient model validation and revision.

907-Pos Board B707

A mathematical Model of Signaling in Podocyte Foot Processes

Cibele V. Falkenberg, Michael L. Blinov, Leslie M. Loew.

The first stage of blood filtration occurs in the glomerulus, where water and other small sized molecules are freely filtered into the urinary space while albumin and larger proteins are retained in the blood capillaries. Maintenance of the size-selective glomerular filtration barrier is regulated by highly differentiated cells, podocytes, their cell-cell interactions in the slit diaphragm and the cell-GBM (glomerular basement membrane) interaction of the podocyte foot processes. Mutations of the nephrin gene (NHPHS1) triggers actin reorganization, loss of the podocyte functional morphology and massive proteinuria. The glomerular tissue is challenging to study in vitro, because podocytes from isolated glomeruli undergo de-differentiation within hours, while cultures of stabilized cell lines never complete differentiation. Therefore, to provide insight into how the integrity of the filtration barrier is dynamically maintained, we have developed a mathematical model of the podocyte that preserves the spatial organization found in the intact glomerulus, focusing on the nephrin pathway. Nephrin has four binding sites phosphorylated by the same mechanism (nephrin clustering and Fyn phosphorylation) that can trigger the formation of actin branches via Arp2/3. Importantly, Nck (a scaffold that coordinates F-actin nucleation), PLCγ1 (an enzyme that hydrolyzes PIP_2) and podocin (important for nephrin localization) all compete for one of the phosphorylation sites on nephrin. The model includes complex formation around nephrin and several proteins involved in actin cytoskeleton remodeling, such as PI3K and Fyn. We use rule-based modeling to account for multiple complexes and phosphoforms and investigate the signaling on the level of domain-domain interactions. The model is associated with the spatial organization of the foot processes, incorporating localization effects. (supported by NIH grant TRO1DK087650)

908-Pos Board B708

Is Intracellular ph a Master Clock for the Events of Mitosis?

Lucian J. Gagliardi.

Experiments have shown that the intracellular pH of many cell types rises to a maximum at the onset of mitosis, subsequently decreasing 0.3 to 0.5 pH units from typical peak values of 7.3 to 7.5 measured during prophase [1]. This result, and observations that tubulin net charge depends strongly on pH, varying quite linearly from -12 to -28 (electron charges) between pH 5.5 and 8.0 [2,3], could be significant for microtubule (MT) dynamics during mitosis. Studies have shown that MT dynamics is sensitive to pH, with MT growth favored by higher intracellular pH values [4-6]. Given the above observations collectively, it seems reasonable to assume that the shift from the dominance of MT growth during prophase, and to a lesser extent during prometaphase, to a parity between MT polymerization and depolymerization during metaphase chromosome oscillations could be attributed to the gradual downward intracellular pH shift during mitosis that is observed in many cells. Thus the timing and sequencing of prophase, prometaphase, and metaphase chromosome motions may be understood as an increase in the MT disassembly to assembly probability ratio resulting from a continuously falling intracellular pH [7,8].

[1] See for ex., Amirand, C. et al., Biol. Cell, vol. 92:409 (2000). [2] Sackett, D., Banff Workshop, Molecular Biophysics of the Cytoskeleton, Banff, Alberta, Canada, Aug. 25-30, 1997. [3] Tuszynski, J.A. et al., J. Theor. Biol., vol. 174:371 (1995). [4] Schatten, G. et al., Eur. J. Cell Biol., vol 36:116 (1985). [5] Kirschner, M.W., J. Cell Biol., vol.88:604 (1980). [6] Deery, W.J. and Brinkley, B.R., J. Cell Biol., vol. 96:1631 (1983). [7] Gagliardi, L.J., Phys. Rev. E 66:011901 (2002). [8] Gagliardi, L.J. "Electrostatic Considerations in Mitosis", iUniverse Publishing Co., 2009.

909-Pos Board B709

Noise and Crosstalk in the Two Quorum Sensing Channels of Vibrio Fischeri

Stephen J. Hagen, Pablo Delfino Pérez, Joel T. Weiss.

Bacteria use the signaling mechanism known as quorum sensing (QS) to detect and respond to their population density. By releasing a diffusible molecule (an autoinducer) into their environment, they can use the local concentration of this molecule as an indicator of population density and regulate phenotype accordingly. In many bacterial species the QS regulatory pathways are complex, receiving inputs from several different autoinducers. Therefore it is important to understand how bacteria integrate multiple signals and how the signal-to-noise property of each autoinducer channel affects that of other channels.

We have studied the role of noise and crosstalk between two QS signals in *Vibrio fischeri*, a luminescent bacterium that colonizes the light organ of a number of fish and squid species. *V.fischeri* produces a 3-oxo-C6 homoserine lactone autoinducer (3OC6HSL) that interacts with its receptor LuxR to activate transcription of the *lux* bioluminescence genes; the bacterium also produces a C8 homoserine lactone signal (C8HSL) that regulates aspects of host colonization. However, the 3OC6HSL regulation of *lux* is not only noisy at the single cell level, but is also subject to strong interference or crosstalk from the C8HSL signal. C8HSL indirectly activates the expression of LuxR while also competitively inhibiting the interaction of 3OC6HSL with LuxR.

We are investigating the effect of crosstalk between 3OC6HSL and C8HSL channels on the noise and sensitivity of the quorum response of individual *V.fischeri* cells. We use a microfluidic approach, where the cells occupy a microscopic chamber in which a continuous flow of medium imposes well-defined gradients and concentrations of exogenous C6HSL and C8HSL autoinducers. Using a chromosomal *gfp* reporter for the *lux* genes we can observe the joint effect of C8HSL and 3OC6HSL on quorum regulation and its temporal and cell-to-cell variability.

910-Pos Board B710

A LEGI-Biased Excitable Network Controls Temporal and Spatial Responses to Chemoattractants

Yuan Xiong, Chuan-Hsiang Huang, Pablo A. Iglesias, Peter N. Devreotes.

Many cells have the ability to respond to external chemical stimulus, a process referred to as chemotaxis. Critical for many biological and physiological processes, the overall pathways that regulate chemotaxis are evolutionarily conserved, and the chemotactic behavior is similar among most eukaryotic cells. When there are no chemical cues, cells migrate randomly. Upon spatially uniform constant stimulus, they stop and round up, and localized patches of activity appear later as cells spread. Finally cells adapt and resume random migration. On the other hand, when exposed to a gradient of chemoattractant, cells are able to continuously steer their pseudopodia activity, thus their motility, toward the higher side.

Many models have been developed and can capture some features of chemotaxing cells, but none has brought together the diverse observations into a unified scheme. Here we propose the local-excitation, global-inhibition (LEGI) biased excitable network hypothesis, and formulate a model that simulates most of the temporal and spatial responses to chemoattractants. More specifically, our model couples the LEGI mechanism, which can partly predict the responses to step and gradient stimuli, with a downstream reaction-diffusion based noise-driven excitable system, which is simplified as a two-component activator-inhibitor model that controls the cytoskeletal activity. This LEGI-biased excitable network can explain the complex response kinetics, the sensitivity to shallow gradients, and the recently observed propagating waves of various molecular components in chemotaxing cells. Furthermore, by perturbing model parameters, our model is able to generate distinct behaviors consistent with known classes of mutants.

Our model provides a framework to understand how newly appreciated excitable behavior in cells can be regulated by external cues and satisfactorily accounts for most of the responses of chemotactic cells to spatial and temporal stimuli, as well as motivate experimentations and interpret new observations.